

# PATENT SPECIFICATION

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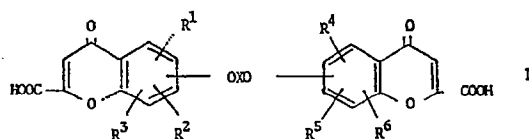
- (72) Inventors HUGH CAIRNS  
 JOHN EDWARD WILLIAM TILLMAN and  
 DEREK WILLIAM WHYMARK

## (54) PROCESS FOR THE PRODUCTION OF BIS-CHROMONE-2-CARBOXYLIC ACIDS, AND INTERMEDIATES THEREFOR

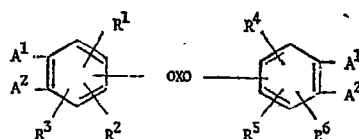
(71) We, Fisons Limited, a British Company, of Harvest House, Felixstowe, Suffolk, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a new process for the production of chromone-2-carboxylic acids.

According to our invention we provide a process for the production of a compound of formula I,



in which R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are the same or different and each is a hydrogen or halogen atom or an alkyl, hydroxy, alkoxy or substituted alkyl or alkoxy group (for example a hydroxyalkoxy, alkoxyalkoxy or carboxyalkoxy group), and X is a saturated or unsaturated substituted or unsubstituted hydrocarbon chain which may be interrupted by a carboxylic or heterocyclic ring, or one or more oxygen atoms or carbonyl groups, and pharmaceutically acceptable derivatives thereof, which comprises cyclising a compound of formula II,



II

in which R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and X are as defined above, each pair of groups A<sup>1</sup>, A<sup>2</sup> represent the pair of groups —OH and —COCH<sub>2</sub>COCOOH, or the chain —O—C(COOH)=CH—CO— or a derivative (e.g. ester) thereof, provided that at least one of the pairs of groups A<sup>1</sup>, A<sup>2</sup> represent the pair of groups —OH and —COCH<sub>2</sub>COCOOH, and where desired or necessary converting the resulting compound of formula I to a pharmaceutically acceptable derivative thereof or vice versa.

The cyclisation may be carried out by heating, preferably in the presence of an acid, e.g. hydrochloric acid, and in a solvent which is inert under the reaction conditions, e.g. ethanol. The reaction may be carried out at from about 20° to 150°C.

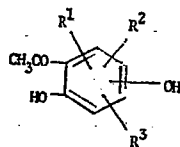
[Price 25p]

It will be appreciated that the group  $-\text{COCH}_2\text{COCO}_2\text{H}$  may also exist in the corresponding tautomeric form  $-\text{COCH}=\text{C}(\text{OH})\text{CO}_2\text{H}$ . The compound of formula II may thus also be used in such a tautomeric form. The compound of formula II may also be used in the form of a salt, for example an alkali-metal salt, thereof.

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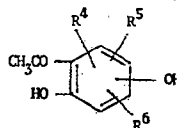
Compounds of formula II may be made by reacting a compound of formula III,

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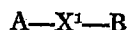
III

with a compound of formula IV,



IV

and a compound of formula V,

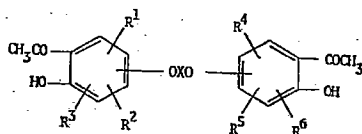


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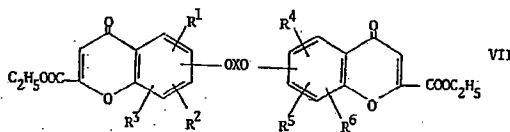
in one or more stages to form a compound of formula VI,

V



VI

converting the compound of formula VI to a compound of formula VII,



VII

15

by reaction with diethyl oxalate in a manner known *per se*, and then carefully treating the compound of formula VII, or its hydrolysis product of formula I, with dilute sodium hydroxide at approximately ambient temperature.

15

$\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$  and  $\text{X}$  in the formulae III, IV, VI and VII being as defined above,

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A and B in formula V being the same or different and each being a group capable of reacting with an  $-\text{OH}$  group to form an ether linkage, and

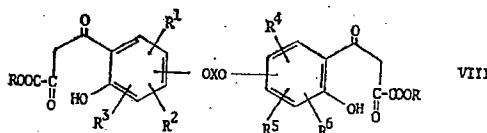
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$\text{X}^1$  in formula V being such that with the residues of A and B it forms an X group.

25

Alternatively the compound of formula II may be made by treating a compound of formula VIII,

25



VIII

in which  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$  and  $\text{X}$  are as defined above, and R represents an alkyl group, with alkali under controlled conditions, for example by extracting a chloroform solution of a compound of formula VIII with aqueous alkali.

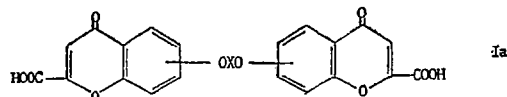
The compounds of formula I, and the intermediates therefor, may be recovered from the reaction media in which they are produced using conventional techniques.

The compounds of formulae III, IV and V are either known or may be made from known compounds using known techniques.

The compounds of formula I are useful in the treatment of allergic asthma. Pharmaceutically acceptable derivatives of the compounds of formula I include pharmaceutically acceptable salts esters and amides thereof, particularly preferred are the pharmaceutically acceptable salts, e.g. the sodium salt.

Where  $R^1$  to  $R^6$  are carbon containing substituents it is preferred that they contain from 1 to 8 carbon atoms. When  $R^1$  to  $R^6$  are halogen they may be, for example, chlorine or bromine. X may be, for example, a hydrocarbon chain which may be substituted by chlorine, bromine, hydroxy or alkoxy 0 to 6 or which may be interrupted by a 5 or 6 membered carbocyclic or nitrogen or oxygen containing heterocyclic ring.

Preferred compounds of formula I are those of formula Ia,



in which X is as defined above.

It is also preferred that X is a polymethylene chain containing from 3 to 7 carbon atoms, which chain is optionally substituted by an —OH group. The invention is of advantage in that it enables a pure product to be made and in that it produces an acid and not an ester product. The hydrolysis of an ester of a compound of formula I to an acid of formula I can lead to opening of the chromone ring and contamination of the product with ring opened material.

The invention is illustrated, but in no way limited by the following Examples in which the parts are by weight.

#### Example 1

Cyclisation of 1,3-bis[2-(3-carboxy-1,3-dioxopropyl)-3-hydroxyphenoxy]-2-hydroxypropane

A solution of 0.5 parts of 1,3 - bis(2 - carboxychromon - 5 - yloxy) - 2 - hydroxypropane disodium salt in 100 parts of 0.1N aqueous sodium hydroxide solution was kept at 25°C in a water bath for 16 hours. The solution was then acidified with dilute hydrochloric acid in the presence of ether. After shaking the ethereal layer was separated, dried over sodium sulphate and evaporated to leave 0.06 parts of 1,3-bis[2 - (3 - carboxyl - 1,3 - dioxopropyl) - 3 - hydroxyphenoxy] - 2 - hydroxypropane. 0.06 parts of this bis-1,3-dioxo acid were dissolved in 10 parts of ethanol containing 0.2 parts of concentrated hydrochloric acid. After a few minutes 0.04 parts of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane were precipitated as a colourless solid m.p. 216—7°C (d).

#### Example 2

Cyclisation of 1,3-bis[4-(3-carboxy-1,3-dioxopropyl)-3-hydroxyphenoxy]-2-hydroxypropane

A solution of 0.5 parts of 1,3 - bis(2 - carboxychromon - 7 - yloxy) - 2 - hydroxypropane disodium salt in 1000 parts of 0.3N aqueous sodium hydroxide was kept at 25°C for 90 minutes. The solution was then acidified with dilute hydrochloric acid in the presence of ether. After shaking, the ether layer was separated, dried over sodium sulphate and evaporated to yield a yellow residue of 1,3-bis[4-(3-carboxy-1,3-dioxopropyl) - 3 - hydroxy - phenoxy] - 2 - hydroxypropane. This yellow substance was dissolved in 10 parts of ethanol containing 0.2 parts of hydrochloric acid. On warming to 50°C a white precipitate of 1,3 - bis(2 - carboxychromon - 7 - yloxy) - 2 - hydroxypropane was produced. This was identified by comparison of the infra red spectrum with that of an authentic specimen.

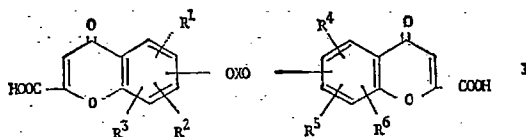
#### Example 3

Production of 1,3-bis[2-(3-carboxy-1,3-dioxopropyl)-3-hydroxyphenoxy]-2-hydroxypropane

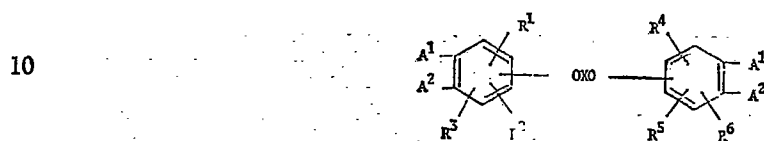
A solution of 0.0006 parts of 1,3 - bis[2 - (3 - ethoxycarbonyl - 1,3 - dioxopropyl) - 3 - hydroxyphenoxy] - 2 - hydroxypropane in 3 parts of chloroform was extracted with a 0.1N solution of sodium hydroxide. The aqueous extract had the same ultraviolet spectrum as an aqueous alkaline solution of the title compound produced as in Example 1.

## WHAT WE CLAIM IS:—

1. A process for the production of a compound of formula I,



5 in which  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and  $R^6$  are the same or different and each is a hydrogen or halogen atom or an alkyl, hydroxy, alkoxy or substituted alkyl or alkoxy group and X is a saturated or unsaturated substituted or unsubstituted hydrocarbon chain which may be interrupted by a carbocyclic or heterocyclic ring, or one or more oxygen atoms or carbonyl groups, and pharmaceutically acceptable derivatives thereof, which comprises cyclising a compound of formula II,



II

15 in which  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$  and X are as defined above, each pair of groups  $A^1$ ,  $A^2$  represent the pair of groups  $-\text{OH}$  and  $-\text{COCH}_2\text{COCOOH}$ , or the chain  $-\text{O}-\text{C}(\text{COOH})=\text{CH}-\text{CO}-$  or a derivative thereof, provided that at least one of the pairs of groups  $A^1$ ,  $A^2$  represent the pair of groups  $-\text{OH}$  and  $-\text{COCH}_2\text{COCOOH}$ , and where desired or necessary converting the resulting compound of formula I to a pharmaceutically acceptable derivative thereof or vice versa.

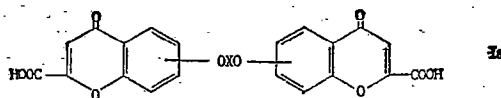
2. A process according to Claim 1, wherein the cyclisation is carried out in the presence of an acid.

20 3. A process according to Claim 1 or Claim 2, wherein the cyclisation is carried out in a solvent which is inert under the reaction conditions.

4. A process according to any of the preceding claims, wherein the reaction is carried out at a temperature of from  $20^\circ$  to  $150^\circ\text{C}$ .

5. A process according to any of the preceding claims, wherein the compound of formula II is used in the form of a salt thereof.

25 6. A process according to any of the preceding claims, wherein the compound of formula I is of formula Ia,



in which X is as defined in Claim 1.

30 7. A process according to any of the preceding claims, wherein X is a polymethylene chain containing from 3 to 7 carbon atoms, which chain is optionally substituted by an  $-\text{OH}$  group.

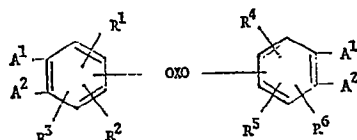
8. A process according to any of the preceding claims, wherein the compound of formula I is 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane.

9. A process according to Claim 1 and substantially as hereinbefore described.

35 10. A process according to Claim 1 and substantially as hereinbefore described in Example 1 or Example 2.

11. A compound of formula I whenever produced by a process according to any one of the preceding claims.

12. A compound of formula



in which  $R^1, R^2, R^3, R^4, R^5, R^6$  and  $X$  are as defined in Claim 1, and each pair of groups  $A^1, A^2$  represent the pair of groups  $-\text{OH}$  and  $-\text{COCH}_2\text{COCOOH}$ , or the chain  $-\text{O}-\text{C}(\text{COOH})=\text{CH}-\text{CO}-$ , provided that at least one of the pairs of groups  $A^1, A^2$  represent the pair of groups  $-\text{OH}$  and  $-\text{COCH}_2\text{COCOOH}$ .

C. B. CRAIG,  
Chartered Patent Agent,  
Agent for the Applicants,  
Fisons Limited,  
Fison House, Princes Street,  
Ipswich Suffolk.

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